

Reviews/Analyses

Quality control of BCG vaccine by WHO: a review of factors that may influence vaccine effectiveness and safety

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WHO oversees the quality control of BCG vaccine via a system that includes regular testing of products by in vitro methods and clinical trials. Three parent strains of BCG (Glaxo-1077, Tokyo-172, and Pasteur-1173P2) account for over 90% of the vaccines currently in use worldwide. Important characteristics of the vaccine preparations are summarized here, along with their physical-chemical properties. In instances where diagnostic criteria for tuberculosis are stringent, there is no evidence that when administered to newborns different preparations of BCG vaccine exhibit different efficacies; however, the incidence of BCG-associated adverse reactions does correlate with the type of preparation. Other factors, including dose, administration technique, and recipient characteristics are also important in determining vaccine-associated reactions.

Background history

The involvement of WHO in quality control of BCG vaccines began in 1948 when the Organization took over responsibility for the large-scale international BCG vaccination programmes that were using liquid vaccine. Since then, the system for quality control of BCG vaccine has undergone changes, as have the methods to produce and test it. Here, we summarize the information gained from studies on the efficacy of, adverse reactions to, and quality control of BCG vaccines to provide a reference for activities aimed at maintaining and improving their quality.

In 1974 the Twenty-seventh World Health Assembly reaffirmed the importance of quality control of BCG vaccines and recommended that all member countries producing or importing BCG vaccine use the international quality control system set up by WHO "until they have established a competent national

control service."^a All producers of freeze-dried vaccine supplied by or through UNICEF were already using this system, which consisted of evaluation in international reference laboratories and centres both in the laboratory and by clinical testing.^b

The system is based on keeping the number of BCG production and control centres to a minimum. Quality control testing is coordinated by the BCG Section of the Quality Control Department of the State Serum Institute, Copenhagen; training of staff in the production and control of BCG vaccine is also carried out in Copenhagen.

This international system was set up by the WHO Tuberculosis unit, but in 1976 responsibility for *in vitro* assays was transferred to the WHO Biologicals unit, and, in December of 1982, all responsibility for international quality control of BCG was transferred to the latter unit. The State Serum Institute has continued to coordinate quality control of BCG with the assistance of three to four collaborating laboratories in Asia and Europe and of the Pan American Zoonoses Center

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^a Resolution WHA27.54. *Handbook of resolutions and decisions of the World Health Assembly and the Executive Board, volume II, 1973-1984*. Geneva, World Health Organization, 1985, p. 154. In the future, it is expected that responsibility for quality of individual vaccines will be shifted almost exclusively to national control authorities.

^b See WHO-sponsored international quality control of BCG vaccine. WHO/TB/Technical Guide/77.8.

(CEPANZO), Buenos Aires, which serves as a reference centre for the Region of the Americas and performs the coordinating, testing, and training functions for this region with advice from Copenhagen.

The State Serum Institute performs the following tasks: coordinates the international quality control system; provides technical advice to national BCG laboratories at the request of WHO; provides training in BCG vaccine production and quality control in consultation with the WHO Tuberculosis unit; distributes references and seed lots of BCG vaccine; tests candidate BCG vaccines from producers; and tests samples from vaccine lots supplied to national immunization programmes through or by UNICEF. For each lot of BCG vaccine supplied to UNICEF, the international quality control system at present consists of a review of summary protocols, testing of random samples, and clinical testing of products. The WHO procedure for evaluating the acceptability of lyophilized BCG vaccines offered for sale to UNICEF for use in the Expanded Programme on Immunization (EPI) has already been described (1).

Quality control testing

There is consistent evidence from several clinical trials that the BCG seed lots used to produce vaccines which have protective efficacy in laboratory animals and induce tuberculin sensitivity in humans are effective against disseminated disease and meningitis in childhood tuberculosis, and probably to a lesser degree also against other forms of tuberculosis in children (2-7). At present, however, there is no laboratory test that correlates with the protective efficacy of a given BCG vaccine preparation.

For this reason, the strategy employed has been to evaluate the protective efficacy of several different preparations of BCG vaccine through careful clinical trials, using vaccines whose safety and *in vitro* characteristics have already been verified. Once vaccine efficacy in humans is demonstrated, repeated measurement of tuberculin sensitivity and lesion size as well as various *in vitro* tests on cultured BCG bacteria are used to verify that the lots of vaccine grown from these preparations are being reproduced satisfactorily. The laboratory tests are thus designed to verify that successive batches are indeed uniform or vary within only narrow limits. In addition, the WHO Requirements for Dried BCG Vaccine (8) suggest to the national control authority the possible need to conduct trials in tuberculin-negative human subjects to determine the optimum content of BCG organisms whenever there is a change in manufacturing procedure. It is required, in any case, that manufacturers conduct such studies in children on at least one batch each year.

In vitro tests

Several *in vitro* tests for BCG vaccine have been described.^c One such test, which determines the number of culturable particles, provides the most information on vaccine viability. The test is, however, subject to considerable variability, depending on the culture media used, the components of the media, and the test procedures. A laboratory therefore needs to establish consistency in the test performance and to be able to relate the numbers of BCG particles determined for a particular vaccine to clinical effects such as scar size, post-vaccination tuberculin hypersensitivity, and incidence of common toxic effects such as regional lymphadenitis.

A rapid test for viability is based on measurements of bioluminescence, which, if the conditions are adjusted so that the bioluminescence is proportional to the adenosine triphosphate content, is a reliable marker for living cells. This test is useful once the mean content of adenosine triphosphate per culturable particle has been estimated for a given vaccine strain.

Examination of the colony morphology of cultures of BCG vaccine also provides useful information.

Vaccine viability

The viability of a given BCG vaccine (the proportion of living and dead bacilli) is an important determinant of its characteristics. The final product is filled in containers according to a standard bacterial mass, which is estimated by weight or opacity. The percentage of total bacterial particles that is culturable is then determined. This percentage is subject to further decrease after freeze-drying.

The extent of the local reaction to BCG vaccination is proportional to the total bacterial mass, while the level of tuberculin sensitivity is related to the number of culturable particles.^d The Tokyo strain of BCG vaccine generally has a high viability and a high resistance to freeze-drying (9). Also Gheorghiu et al. have reported a Pasteur-strain vaccine prepared in dispersed culture that has a high viability compared to the classically grown strain (10).

Vaccine thermal stability

The degree of thermal stability of each final lot of BCG vaccine is an important characteristic, and under WHO requirements the number of culturable particles in a vaccine after incubation for 28 days at 37 °C must

^c See: *In vitro assays of BCG products*. WHO/TB/Technical Guide/77.9; and *Manual of tests on vaccines in the Expanded Programme on Immunization*. WHO unpublished document BLG/UNDP/82.1 Rev.1.

^d See footnote b, p. 93.

not be less than 20% of that in samples of the same vaccine stored at 4 °C.

There have been several studies of the heat stability of freeze-dried vaccines (9, 11). Some of the differences in thermal stability can be attributed to the growth characteristics of the vaccine (9), while others are clearly related to the preparation and packaging of the freeze-dried vaccine (11). Ladefoged (personal communication, 1989) has recently compared the characteristics of the freeze-dried Copenhagen vaccine stored in ampoules or vials. The vaccines were prepared, dispensed from the same apparatus, and freeze-dried, the only difference between the products being that the ampoules were sealed under vacuum, while the vials were sealed after being filled with nitrogen. No difference in viability or in heat stability was found immediately after freeze-drying. For a few lots, however, after 3 months' storage at 4°C, the thermal stability of the vaccine in ampoules was slightly better than that in vials. These studies have now been extended to 12 months, and over this period of time the freeze-dried BCG vaccine in vials exhibited satisfactory stability in the case of this particular product. This stability is, however, strongly dependent on the quality and treatment of vials and stoppers and must be determined independently for each vaccine preparation.

Delayed-type hypersensitivity in animals

An analysis of the potency of BCG vaccine in animals is beyond the scope of this review. Attention is drawn, however, to studies that have compared a number of preparations using *in vivo* methods (12, 13). Animal experiments show that cellular immune responses induced under experimentally controlled conditions

are higher for the traditionally "stronger" vaccine preparations, i.e., Pasteur and Copenhagen (9). These are also the preparations that give rise to a higher incidence of adverse reactions such as suppurative lymphadenitis. However, there is evidence that the reproducibility of assays of BCG protective efficacy in different animal test systems is not sufficiently good to permit relative judgements of quality between vaccine preparations (69).

Characteristics of current BCG preparations

In order to determine which preparations of BCG vaccine are currently in use and their characteristics, we requested information from 15 manufacturers included in the WHO 1984 List of Availability of Vaccines and Sera, who had responded with information for the 1989 list. Responses were received from all those contacted, and some of the data obtained are summarized in Table 1.

In Table 1 it should be noted that the range of the number of culturable particles per dose is a compilation of the numbers reported by all producers of a vaccine that was prepared from a particular parent strain. Therefore, a wide range in the number of culturable particles per dose does not necessarily imply a wide variability of the product. However, in view of the dose dependence of both induced tuberculin sensitivity and reactogenicity, it is clear that an important characteristic of a vaccine is its homogeneity expressed as the range of the number of culturable particles. WHO requirements reserve the setting of the limit of inhomogeneity allowed to national control authorities. Those vaccines in Table 1 with relatively low numbers of culturable particles

Table 1: Summary of some of the responses obtained from manufacturers of BCG vaccine

Parent strain	No. of manufacturers	Reported number of culturable particles per dose	Stabilizer	Total production, (approximate number of doses per year)
Pasteur-1173P2	6	37 500-500 000 ^a	Sodium glutamate, ± dextran, glucose	59.0 million
Copenhagen-1331	3	150 000-300 000 ^b	Haemacel, glucose, or monosodium glutamate	3.0 million
Glaxo-1077	2	200 000-1 million	Dextran, dextrose, or albumin	40.0 million
New York	1	525 000-1.125 million ^c	7.5% Lactose, salts	100 000
Tokyo-172	1	3 million	Sodium glutamate	54.0 million
Montreal	2	200 000-3.2 million ^b	Dextran, sucrose, or monosodium glutamate	9.0 million

^a Four of six suppliers recommend a half or smaller dose for infants.

^b Half dose recommended for infants.

^c Three-quarters dose recommended for infants.

per dose (e.g., Pasteur and Copenhagen) are more reactogenic than those with higher numbers (e.g., Tokyo).

The composition of the stabilizer is important since it contributes to the ease of reconstitution as well as to stability properties. Vaccine stabilized with monosodium glutamate may be more difficult to reconstitute, while the presence of albumin, although it is readily soluble, may lead to foaming of the product during reconstitution.

The vast majority of BCG vaccine used is limited to three preparations—Pasteur, Glaxo, and Tokyo. Accordingly, we will concentrate on the characteristics of these preparations, although others will also be dealt with. A summary of the history of four of the most widely used strains, Pasteur-1173P2, Tokyo-172, Copenhagen-1331, and Glaxo-1077, is given by Osborn (14), while an extensive summary of the history of the Pasteur strain is reported by Gheorghiu et al. (15).

Physical-chemical characteristics

A number of different studies have appeared in which the physical-chemical characteristics of various preparations of BCG vaccine have been compared, including biochemical and immunological analyses of secreted proteins and chromatographic analyses of lipid production (Table 2). It should be noted that vaccine preparations, though referred to as being of one or another strain, are complex mixtures of a variety of different BCG mycobacteria. Methods of production may influence the composition of these mixtures and the same "strain" of BCG may differ among production facilities.

MPB70 is a unique BCG-specific antigen that elicits a delayed skin reaction in guinea-pigs sensitized with viable BCG cells. Guinea-pigs sensitized with heat-killed BCG do not show delayed-type hypersensitivity to MPB70 (16). MPB70 has a relative molecular mass of 15 100, contains no sugar moieties, and comprises up to 10% of the total protein content of the culture medium of the Tokyo strain of BCG, although it is present only in trace quantities in other strains (17). Table 2 shows that strains of BCG fall into two groups according to the content of this protein, with the Glaxo strain being distinctive in containing an intermediate amount. This grouping is also reflected by analysis of the level of dimer antigen of relative molecular mass 46 000 (18) or of that of antigen 15 (19) and by secretion of methoxymycolate (20–22). It is not clear whether all of these phenomena are related to the expression of one protein, which is present in different forms because of its breakdown. It is interesting to note that the Swedish strain produces methoxymycolate irrespective of whether it is prepared in Copenhagen or in Gothenburg (20), i.e., that this characteristic is present under at least two different production conditions.

In contrast production of mycoside B (glycosyl-phenolphthiocerol dimycoserates) appears to be associated with colony morphology (21), both characteristics having been observed, based on studies on four preparations, to vary with the production method. It is, however, not yet known to what extent these laboratory characteristics correlate with the protective efficacy of and adverse reactions to BCG vaccine.

Table 2: Some characteristics of strains of BCG vaccine

Strain	Characteristic:				
	MPB70 ^a	Dimer (M _r = 46 000) ^b	Methoxymycolate ^c	Mycoside B ^d	Colony morphology ^d
Tokyo-172	++	+	+	+	Spreading
Moreau (Brazil)	++	+	+	ND ^e	ND
Russian	++	+	+	ND	ND
Swedish	++	ND	+	ND	ND
Glaxo-1077	+	±	—	—	Nonspreading
Tice	—	—	ND	ND	ND
Copenhagen-1331	—	—	—	+	Spreading
Pasteur-1173P2	—	—	—	+	Spreading
Beijing	— ^f	ND	—	ND	ND
Prague	ND	—	—	—	ND
Dutch	ND	—	ND	ND	ND
Indonesian	ND	—	ND	ND	ND
Dakar	ND	—	ND	ND	ND

^a Data from ref. 17. ++ = 50–100% of the amount found in the Tokyo strain; + = 1–10% of the amount found in the Tokyo strain; — = < 10% of the amount found in the Tokyo strain.

^b See ref. 18. + = present; — = absent; ± = present in trace amounts.

^c See ref. 20. ^d See ref. 21. ^e ND = not determined. ^f See ref. 22. ^g See ref. 16.

Efficacy in producing tuberculin sensitivity in newborn children

One measure of the potency of a BCG vaccine is the post-vaccination delayed sensitivity to tuberculin (PVS) induced in children who are tuberculin-negative before vaccination. In a study by Vallishayee et al., 11 different BCG preparations were produced under uniform conditions and tested for PVS using two units of tuberculin 9–11 weeks after vaccination (23). With the exception of the Prague strain, there was little difference in the mean PVS induced by these preparations.

The PVS to tuberculin depends, of course, on the method of measurement; both the dose of tuberculin used and the interval between vaccination and testing also affect the sensitivity of the test. A number of studies of newborn children have measured the ability of different vaccines to produce PVS. The following strains produce a high proportion of conversions in neonates: Glaxo (24, 25), Tokyo (25), Pasteur (26), and Copenhagen (26, 27). In Nigeria one study with the Glaxo strain reported that satisfactory tuberculin sensitivity was induced even in pre-term infants (28). However, some studies have shown a less than optimal result among Asian children (29–31), although they may still have been protected against tuberculosis. A trial by Fillastre et al. showed that the same Pasteur freeze-dried vaccine produced a lower tuberculin hypersensitivity among Indonesian (64%) than among French children (88%), which suggests that the living conditions and previous atypical mycobacterial infections of the children, as well as genetic characteristics, may be important in determining BCG immunogenicity (32).

A clear vaccine dose–response relationship for the magnitude of the PVS has been demonstrated (33, 34); however, for doses greater than the lowest that produces PVS in most vaccinees, increasing the dose yields only a small increase in the size of induration. In other words, the slope of the dose–response curve is small, and may vary with vaccine preparation.

While it is generally accepted that delayed hypersensitivity to tuberculin after natural infection is associated with partial protection against reinfection with tuberculosis, the relation between PVS and the protective efficacy of BCG has not been well studied.

Efficacy in preventing tuberculosis in newborn children

The least ambiguous way to assess the protective efficacy of a vaccine is through a randomized, double-blind, placebo-controlled trial. Eight randomized community trials have been reviewed by Clemens et al. (35). The observed vaccine efficacy ranged from 0% to 80%. This variability may have arisen because of the

prevalence of infection with non-tuberculosis mycobacteria, variation in the intensity of exposure to tuberculosis, questionable potency of some of the BCG preparations tested, and differences in the intrinsic host resistance to tuberculosis. However, only three prospective community trials have evaluated the efficacy of BCG vaccine given at birth (36), although the standard immunization schedule of the WHO Expanded Programme on Immunization recommends that the vaccine be given at this time. A randomized trial carried out among newborns in Hong Kong compared the efficacy of the Glaxo and Pasteur strains using 0.3 mg/ml of Glaxo vaccine and 0.1 mg/ml of Pasteur–1173P2 (both produced by Japan BCG Laboratory).^{*} Of the 162 953 newborns who received the vaccine intradermally, 3.43 per 10 000 of those given the Pasteur vaccine developed tuberculosis within a 4-year period, compared with 4.55 per 10 000 of those given the Glaxo vaccine, a small but statistically significant difference. Absolute efficacy could not be measured, however, since there was no unvaccinated control group. Also, no details of case ascertainment were provided.

Some retrospective studies (e.g., those carried out by Curtis et al. (6)) have reported high vaccination efficacies, and WHO has recently sponsored studies to evaluate the protective efficacy of BCG vaccination of infants or children by case–control (3, 37) and contact studies (38).

In evaluating such studies, it is important to consider the following: the rigour with which the case definition was formulated and applied; the vaccination coverage; the assessment of vaccination status; and the comparability of vaccinated and unvaccinated groups with respect to tuberculosis exposure and infection, ability to mount a cell-mediated immune response, and access to accurate diagnosis of tuberculosis. Cases and controls should, therefore, be comparable with respect to age, sex, race or ethnic background, and socio-economic status. In only a few studies have all these features been considered for neonates. Two of these are the investigations reported by Tidjani et al. (39) in Lomé, Togo, and by Miceli et al. (40) (also discussed by Smith (37)) in Buenos Aires, Argentina, both of which show a high protective effect of BCG vaccination (60–70%) and an even higher efficacy against more severe forms of tuberculosis for which diagnostic criteria are more stringent.

Unfortunately, only one of these two studies gives

^{*} Chan, S.L. et al., Comparison of the efficacy of two strains of BCG vaccine for the prevention of tuberculosis among newborn children in Hong Kong. Paper presented at the XXXVI Conference of the International Union against Tuberculosis, Singapore, 4–7 November 1986.

information on the type of vaccine used. However, several others do provide this information, thus enabling the strain-specific efficacy to be inferred. Table 3 summarizes the data from such studies (41–44). Two other studies, referred to by Smith (37), report a protective efficacy of 74% and 89% against tuberculous meningitis in Brazil, where the Moreau strain has been used for many years. Finally, another study mentioned by Smith (37) reported an efficacy of 40% against all forms of the disease and 75% protective efficacy against tuberculous meningitis in Indonesia, where locally produced Pasteur–1173P2 vaccine is used.

A recent re-analysis has been carried out on two case-control BCG efficacy studies of children from Indonesia and Colombia (70). The re-analysis controlled for selection bias by comparing the efficacies of two different BCG preparations used sequentially in each of the trials and thereby permitted assessment of the relative efficacy of the pairs of vaccines used in each trial. The Tokyo preparation appeared to be more effective than preparations derived from the Pasteur or Copenhagen strains in each case. The results were not tested for significance.

The results of these studies therefore indicate that when BCG vaccine is administered to neonates there is no evidence of efficacy differences between various preparations (70).

Adverse reactions in newborn children

The use of BCG vaccine may be associated with a significant number of adverse reactions. However, in developing countries the incidence of these reactions is generally low compared with the risk of contracting tubercular infection, and the most frequent reaction, suppurative lymphadenitis, is usually self-limiting and requires no treatment. In developing countries, the benefits of BCG vaccination thus heavily outweigh the risks. Nevertheless, vaccination of newborns with BCG probably increases the risk of adverse reactions. A number of other factors also affect the frequency of these reactions. One potentially serious consequence, non-completion of the vaccination series by children whose mothers have seen or heard of such reactions, has been very poorly assessed.

Lotte et al. have developed a classification system for BCG complications and provided estimates of their frequency (45). Two such complications, regional suppurative adenitis (Category 1.2) and osteitis (Category 2.6) are discussed below, both because they are relatively more frequent than others (0.1–38 per 1000 and 0.01–330 per million, respectively) and because cases from a number of countries are fairly well documented.

Regional suppurative adenitis (suppurative lymphadenitis).

The incidence of this complication depends on many factors, including the type and concentration of vac-

cine, the age of the vaccinees, and the use of proper intradermal injection technique (46). For example, in Egypt it was reported that 10% of patients vaccinated in public health welfare clinics exhibited adenitis that needed treatment, compared with 0.02% of those who received BCG vaccine in a chest clinic, where it was administered under strict medical supervision to an older population (47). Lotte et al. cite an incidence of 0.1 per 1000 for this complication in Hong Kong, when a low dose of Glaxo vaccine was given to newborn infants, compared with 38 per 1000 in a mass BCG campaign in Algeria, where infants received a high dose (0.1 ml) of Glaxo vaccine (45). At the same time, use of what was reported to be 0.1 ml of Pasteur–1173P2 strain vaccine in maternity wards in Algeria gave an incidence of only 5 per 1000.

In a retrospective study on BCG complications in six countries in Europe, Lotte et al. concluded that the number of viable units injected had an important influence on the risk of regional complications (48). Quast et al. also found a dose-response relationship between the number of culturable particles and the incidence of suppurative lymphadenitis with the Copenhagen–1331 strain used in the Federal Republic of Germany (49). A similar result was observed with the Pasteur strain in Hungary (50). On the other hand, studies in India with the Madras BCG Laboratory vaccine made from the Copenhagen–1331 strain showed that the incidence of complications differed little among newborn infants given half doses and those given full doses (34).

If it is assumed that, in a given country, a consistent immunization technique and a standard vaccine formulation are used, a number of studies report that the incidence of suppurative lymphadenitis changed when one preparation was replaced by another. In Saudi Arabia, the incidence of regional lymphadenitis following BCG vaccination of newborns increased when the only change was the introduction of the Tokyo strain of BCG (51). Similarly, when the Gothenburg strain was replaced by the Copenhagen–1331 strain in the Federal Republic of Germany in 1975, there was an immediate rise (to 1.5% in one area) in the incidence of suppurative inguinal lymphadenitis after immunization of newborns (52). This fell to 0.02% after the dose-response relationship was investigated and the dose subsequently lowered (53). A more recent study in Zaire of an outbreak of axillary and epicondylar abscesses ruled out underlying infection with human immunodeficiency virus (HIV) as a cause, and concluded that it was due to the change of the BCG vaccine to the Pasteur–1173P2 product (54).

Comparative studies in which different vaccines were used simultaneously in the same population also show that the number of complications varies with the manufacturer and preparation of the vaccine. For

Table 3: Summary of the results of some studies on the protective efficacy of BCG vaccine

Place of study and date	Study population	Vaccine used	Type of study	Diagnostic criteria	Recruitment of controls	Ascertainment of vaccination	Comments
Boksburg-Benoni Hospital, South Africa 1972-76 ^a	Blacks; 0-4-year-olds	Tokyo (after October 1972)	TB cohort	Hospital and clinic records; 538 cases	NA ^b	Hospital records	19 cases vaccinated, 0/8 with meningitis. Efficacy > 60% for all forms, 100% TB meningitis
Rangoon Children's Hospital, Myanmar (Burma) July 1982 ^c	0-4-year-olds	Tokyo half-dose	Case-control	WHO scoring system; 311 cases	Hospital controls matched on sex, age and residence	Scar, documents, and parental recall	Efficacy 38% for all forms, 52% TB meningitis, 80% disseminated TB
Israel, 1956-79 ^d	Jewish; 0-12-year-olds	Glaxo (after late 1960s)	TB cohort	Notification by maternal and child health clinic 299 cases	NA	Maternal and child health clinic or hospital card; 86% coverage after 1962	Age- and sex-adjusted efficacy 24% for pulmonary TB, 64% for extrapulmonary TB
Bangkok Central Chest Clinic, September 1981-June 1984 ^e	0-4-year-olds	Mérieux	Contact (retrospective)	WHO scoring system; 218 cases	1506 contacts of TB cases followed. Age, sex, residence, and socioeconomic status determined	Scar, documents	Efficacy 53% for all TB, 72% for bacteriologically confirmed cases
Manitoba, Canada, 1979-83 ^f	Amerindians; 0-14-year-olds	Connaught	Case-control	Clinical, or laboratory evaluation; 71 cases	213 controls, same age and community but not matched, stratified analysis	Records; 72% coverage of confirmed cases	Efficacy > 60% for all TB, 73% for bacteriologically confirmed cases
Lomé, Togo 1983-85 ^g	0-6-year-olds	Glaxo	Contact	WHO scoring system	1421 child household contacts	Records, scars; 82% coverage	Efficacy 61.5%, higher for more severe disease and children under 6 years of age
Seoul, Korea 1984-86 ^h	<5 years	Paris seed lot 1173P2 produced by Japan BCG Laboratory	Contact	WHO scoring system	1293 child household contacts	Scars, vaccination certificates	Efficacy 74% unpublished study

^a See ref. 25. ^b NA = not applicable. ^c See ref. 41. ^d See ref. 42. ^e See ref. 43. ^f See ref. 44. ^g See ref. 39. ^h Jin, B.W. et al., unpublished results, 1989.

example, in a study in Cakovec, Yugoslavia, Bleiker found that the incidence of enlarged axillary nodes was 5.05% among 1601 newborns vaccinated with Dutch BCG vaccine (Pasteur-1173P2 strain), 0.3% among 1871 vaccinated with the Copenhagen-1331 vaccine, and 3.15% among 1594 vaccinated with the Yugoslav product, which was prepared from the Pasteur-1173P2 strain (55).

Gheorghiu et al. report results from Togo in which the incidence of nonsuppurative adenitis was 4.3% among newborns who received the Pasteur-1173P2 vaccine, while this complication was rare among those who received the London F10 strain (56). Upon introduction of good injection technique in Togo, the incidence of adenitis caused by the Pasteur strain fell to 0.44% (56). In Turkey the risk of regional suppurative adenitis among infants who received the Tokyo strain was 0.3 cases per 1000 compared with 1.3 per 1000 among those who received the local vaccine prepared from the Pasteur strain (45).

In Hong Kong the risk of complications, including enlargement of peripheral lymph nodes and abscess formation, was 0.514 per 10 000 infants who received the Pasteur strain compared with none of 81 304 infants who received the Glaxo strain.[†]

It is generally accepted that some preparations are associated with lymphadenitis less closely than others. For example, the Tokyo strain (45) and the Moreau strain in Brazil (57) are rarely associated with this complication, while the Pasteur strain gives rise to a higher incidence (45, 56). The Copenhagen strain has also been reported to cause a relatively higher frequency of lymphadenitis. Although its significance is unknown, this ranking of BCG preparations by reactogenicity has a roughly inverse relationship with protein and methoxymycolate secretion (see Table 2).

A report in 1988 of an outbreak of BCG-associated lymphadenitis in an area with good access to relatively high-quality health services clearly demonstrates the chief determinants of the occurrence of adenitis.[‡] The infants involved were vaccinated at birth, or during the first 2 weeks of life if their birth weight was below 2500 g, with 0.05 ml of either Pasteur-1173P2 strain vaccine (in a new presentation aimed at minimizing the possibility of confusion in reconstituting it) or vaccine of the Glaxo or Tokyo strain. Cases of adenitis were sought by active surveillance, although most were diagnosed retrospectively. A statistically significant difference was found between the incidence of lymphadenitis after vaccination with the Pasteur strain (9.9% of 531 children) and that after

vaccination with the Glaxo or Tokyo strain vaccine (0 of 221 children). Other factors seemed comparable, since the same immunization centres used each of the three vaccines sequentially during the period of 1988 when each was available.

There was also a striking variation in the rates of adenitis between different centres (range, 0% to 17.6%), which was only partly explained by the fact that the centre with the lowest incidence did not give BCG vaccine to any children under 2 weeks of age. Birth weight data, which were available for 500 of the children, had no effect on the incidence of adenitis (χ^2 test, 0.02); however, the vaccination technique may have been important.

In the most complete currently available review of adverse reactions following BCG vaccination, Lotte et al. attempted to collect, evaluate, and tabulate data from all reported cases up to 1983 and showed that the incidence of regional suppurative lymphadenitis varied widely by country and preparation of vaccine used (45). A study in six European countries again indicated that there was a wide difference in the risk of complications by country, from very slight in Romania to 0.6% in Hungary and 1.7% in Yugoslavia—all of which use their respective national preparations of the Pasteur-1173P2 strain (48). A high incidence of regional suppurative adenitis has been reported in France for Pasteur-1173P2 preparations (58); and especially high incidences have been reported following use of this vaccine in Africa (56).

Although it is clear that improved intradermal injection techniques and appropriate adjustment of doses minimize regional suppurative lymphadenitis, which occurs especially with the Pasteur strain, recent data collected in Paris after administration of dispensed-grown Pasteur strain BCG vaccine to newborn infants, under conditions where injection technique was strictly controlled, showed that the incidence of fistulated adenitis was 0–10%, depending on the lot of vaccine used (N. Guerin, personal communication, 1989). For one lot of vaccine, when the concentration (8.8×10^6 particles/ml) was halved by giving a 0.05-mg instead of 0.1-mg dose the incidence of this complication dropped from 10% to 0%. The correlation between the concentration, expressed as the number of culturable particles, and the incidence of fistulated adenitis was fairly good; moreover, the more reactogenic lots had a lower thermal stability.

In considering the evaluations of most of the above-mentioned reports of BCG-associated lymphadenitis, it should be remembered that careful case definitions were rarely made or applied, and that cases were usually sought by passive surveillance only. Small enlarged axillary lymph nodes (pea-sized or less) are commonly palpable after BCG vaccination, and are rarely noted by the mother unless searched for specifically.

[†] See footnote e, p.97.

[‡] Stuckey, J. *Prevalence of BCG-related adenitis in healthy children, Maputo City, Mozambique*. UNICEF report, October 1988.

In summary, differences in the incidence of BCG-associated lymphadenitis arise, *inter alia*, because of the dose given for a particular preparation of vaccine, the age of the recipient, and the technical quality of the intradermal injection of vaccine. Additional determinants, including the method of preparing the vaccine and the characteristics of the recipient population, may also be important.

Osteitis. The mean risk of osteitis following BCG vaccination varies greatly from country to country, with some reporting extremely low incidences (e.g., 0.01 per million in Japan) compared with high elsewhere (e.g., 300 per million among newborns in Finland) (45). An increased incidence of osteitis has occurred in countries where the vaccine or the method used to manufacture it has been changed, as in Czechoslovakia (59) and Sweden (60).

Use of the Prague strain for universal vaccination of the newborn in Czechoslovakia since 1951 coincided with the disappearance of tuberculous meningitis in children and the almost complete disappearance of tuberculosis in children, in general, by 1982 (61). In 1982, however, the Prague was replaced by the Russian strain. The latter had been held to be more immunogenic (23), although Sula et al. reported no substantial differences in the immunogenicity of the Czechoslovak and Russian BCG strains for guinea-pigs (61). The risk of osteitis in Czechoslovakia in 1982–85 rose to 35 per million (48), with many cases bacteriologically confirmed (62). In contrast, no cases were reported in the USSR, where the same strain was used (48).

The dramatic rise in the incidence of osteitis in Sweden and Finland coincided with the replacement in 1971 of the Gothenburg strain of BCG vaccine produced by the Swedish BCG Laboratory in favour of one produced by the State Serum Institute, Copenhagen, which was also based on the Gothenburg strain. Continuous checking of the virulence in animals during manufacture and comparison in guinea-pigs of the two products manufactured in Sweden and Denmark provided no support for the hypothesis that the process of manufacture was responsible for the observed reactions (63).

A retrospective study from 1948 showed that cases of osteitis occurred in Sweden from 1949 onwards (60). The reported incidence was 1 per 40 000 for children born between 1960 and 1969 and 1 per 3 000 to 1 per 4 000 for neonates vaccinated in 1972–75. It should be noted that compulsory notification of BCG reactions to the Swedish Adverse Drug Reaction Committee was instituted during this period, and there was greater publicity about osteitis. However, a recent retrospective study failed to find any reports of BCG osteitis in six European countries, while cases are still being reported in Finland (although at a lower rate),

where the Glaxo vaccine is in use (48). Cases of BCG-associated osteitis have never been notified in the United Kingdom, where the Glaxo vaccine is also in use (48).

The reason for these increases in the incidence of osteitis remains, as yet, unsolved. The impact of several factors—active case-finding, vaccine strain, manufacturing technique, and body site of vaccination—is undoubtedly important; however the available evidence gives no consistent explanation.

Relationship between biological characteristics and vaccine efficacy and reactogenicity

Although vaccine efficacy, as measured by induced tuberculin sensitivity, and vaccine safety, as measured by the incidence of adverse reactions such as BCG lymphadenitis, both show a dose-response relationship, the slopes of these two dose—response plots differ for different preparations. The acceptability of a BCG vaccine preparation depends on the relative slopes of the plots. For the more reactogenic strains, the dose at which good efficacy and low reactogenicity occurs may be more difficult to determine.

In spite of conjectures about the clinical effects of changing the method of producing BCG vaccine, very few reliable data exist. Osborn has shown that while the Pasteur–1173P2 strain appears to be homogeneous with respect to colony morphology, both the Tokyo and Copenhagen strains are heterogeneous, with a minor population that can become major under certain production techniques, causing them to exhibit nonspreading colony morphology like that of the Glaxo strain (14). Abou-Zeid et al. confirmed this observation for four strains prepared in four production laboratories, and correlated the colony morphology with the presence or absence of the lipid mycoside B (21).

The work reported by Osborn and Abou-Zeid et al. suggests that even in those studies where a number of strains prepared in a single laboratory are compared, their characteristics will not necessarily be maintained or be similar (14, 21, 64). Thus the Japanese BCG vaccine generally exhibits spreading morphology, but when prepared by either the Glaxo or the Pasteur method, it shows nonspreading colony morphology (21). Also, the Glaxo strain prepared in Copenhagen (12, 13) or in Paris (9) grew poorly, making it difficult to compare its *in vitro* characteristics with those of other preparations.

Despite the observed correlation between colony morphology and excretion of mycoside B (21), several other properties of BCG vaccines do not correlate well with colony morphology. For example, Gheorghiu & Lagrange have reported that the Glaxo and Tokyo strains grown in their laboratory, both with nonspreading colony morphology, exhibit completely dif-

ferent viabilities and stabilities (9). Moreover, although measures of immunopotency, such as tuberculin sensitivity in guinea-pigs, seem to be higher in the spreading strains, the nonspreading Glaxo strain, as well as the spreading Pasteur strain, gave better protection in mice (9).

In contrast to these mixed results, Gheorghiu et al. have, however, recently described the preparation of a dispersed-grown vaccine that has better immunogenicity, viability, and heat stability than the classical surface-grown Pasteur BCG vaccine and at least 10% nonspreading colony morphology compared with the 100% spreading colony morphology of the classical strain (10). In the population studied, the higher immunogenicity and dose were not accompanied by increased side-effects.

Preliminary data from a trial of this new dispersed-grown Pasteur vaccine among 1588 newborn children in Togo, with different intradermal doses, indicated suppurative lymphadenitis incidences ranging from 0.8%, for the lowest dose, to 8.8%. When a slightly higher dose of the same vaccine was given to schoolchildren in Europe, there were no cases of lymphadenitis among 528 recipients (WHO Tuberculosis unit, unpublished report, May 1987).

The presence or absence of certain antigens and lipids (see Table 2) appears to divide BCG strains into different categories. Again, there is no obvious correlation with either immunogenicity or efficacy, although some of the more attenuated strains (Tokyo, Moreau) produce the MPB70 antigen and methoxymycolates, while those known to be more potent (Copenhagen, Pasteur) do not. It is of interest that the Swedish strain contains methoxymycolate, whether cultivated in Copenhagen or in Gothenburg (20), which suggests that this marker does not change with the production laboratory. Furthermore, this characteristic lipid production did not correlate with a change in colony morphology (21).

A recent study using DNA restriction mapping analysis of BCG preparations shows a division of the BCG strains tested into the same categories as shown in Table 2 for MPB70 expression, with the Swedish, Russian, Tokyo, and Moreau strains in one category, and the Copenhagen and Pasteur in another (65). It is suggested by the authors that the former group is most like the original BCG strain established as an avirulent vaccination strain in 1921.

Recent work on *Mycobacterium leprae* suggests that the cell wall protein is a major contributor to cell-mediated immune reactivity, but that removal of mycolates does not affect this activity (71). It is clear that further studies are required to define those biochemical correlates that are predictive of efficacy and reactogenicity in humans.

Host characteristics and adverse reactions

As reported by Lotte et al. (45), and from many years of programme experience, the main characteristic of immunologically normal hosts that is associated with increased risk of lymphadenitis is an age at immunization of less than 1 month. While the incidence of lymphadenitis among such infants is approximately twice that among those over 3 months of age, there is no evidence for an increased risk of life-threatening reactions in neonates. Thus, EPI recommends that BCG vaccination be carried out at birth.

Despite the mention on some vaccine package circulars, that a birth weight of less than 2500 g is a contraindication to BCG vaccination, there is no good evidence that otherwise normal children who are moderately premature or have low birth weights, but are able to leave the maternity institution, are at any increased risk of toxicity from vaccination at the time of going home. For example, experience in Mozambique indicates that there is no evidence of a higher incidence of complications among infants whose birth weight was below 2500 g.^h

On a number of occasions, the presence of major congenital immune deficiency has been associated with risk of both local and disseminated BCG infection after vaccination, but this has been reviewed elsewhere and will not be further discussed here. However, an important unresolved issue is the effect of symptomatic and asymptomatic infection with HIV on BCG complications.

At present, WHO recommends not to give BCG vaccine to infants with symptomatic acquired immunodeficiency syndrome (AIDS) (66). This recommendation is based on the existence of five cases of disseminated BCG infection that followed vaccination of such children. While the incidence of such complications could not be calculated, it nevertheless seems reasonable to assume a significantly increased risk in children with symptomatic AIDS. The situation is even less clear for children with asymptomatic HIV infection, the condition exhibited by almost all infected neonates considered for BCG immunization in HIV-endemic countries.

One carefully followed cohort of HIV-positive infants (with controls) has been reported from Zaire.ⁱ

^h See footnote g, p. 100.

ⁱ Myula, Mo et al. Response to childhood vaccinations in African children with HIV infection. In: *Program and Abstracts from Fourth International Conference on AIDS, 12-16 June, 1988, Stockholm, Sweden*. Abstract No. 5107.

A cohort of 470 children of HIV-positive mothers and 600 children of HIV-negative age-parity matched mothers was followed for at least one year, after immunization with all EPI vaccines, including BCG at or near birth. No cases of dissemination were observed in either group, and minor complications (adenitis, fistulization) were not significantly different. Also, the two groups did not differ in their rate of tuberculin sensitivity when tested at the age of 12 months. In a second study of cases of BCG adenitis in Rwanda, although the incidence of adenitis could not be calculated directly, there was no evidence of a higher risk in HIV-positive infants compared with the percentage of women of child-bearing age from the same population who were HIV-positive (E. Mercier, personal communication, 1989).

The determinants of the occurrence of BCG osteitis have been discussed above. Taking into account the limitations in the observational data available, it appears that Swedes and Finns may have a substantially higher risk of developing osteitis, even after differences in use of BCG vaccine preparations are taken into account. No other patient variable appeared to be associated with the occurrence of osteitis.

There is convincing observational evidence for a substantial association between risk of local cutaneous reactions (i.e., keloids) and racial group (45).

In summary, the major host characteristics that may influence the incidence of adverse reactions associated with the use of BCG vaccine in EPI programmes are the doubled incidence of adenitis in neonates compared with older infants and children and the increased risk of disseminated reactions (and possibly of local as well) among infants with serious immunodeficiency involving the T-cell-mediated system. In practical terms, the major risk of concern is abnormal T-cell function secondary to HIV infection—although this is rarely present until several months after birth in perinatally infected infants. Thus the existence of endemic HIV infection should provide EPI programme managers with a strong incentive to provide BCG vaccine at or near birth when available evidence does not suggest increased risk of adverse reactions.

Recent reports

Increased incidence of BCG-associated lymphadenitis

As discussed above, the incidence of regional suppurative adenitis (0.1 to 38 per 1000) is a function of the technique used to administer the vaccine (and thus the training of staff), the dose and preparation of vaccine used, and the characteristics of the recipient pop-

ulation. In general, an immunization programme will be damaged if the reported incidence of post-vaccination regional lymphadenitis rises above approximately 1%.

Below is presented a summary of reports of recent outbreaks of BCG-associated lymphadenitis in various parts of the world.

Mozambique. A suspected increase in neonatal lymphadenitis in Maputo, the capital of Mozambique, was reported in March 1987. An investigation of cases revealed enlarged suppurative axillary nodes (67). The incidence of regional lymphadenitis was 1.3% without active case-finding, but rose to 7.4% when active case-finding was utilized. During the preceding year, the type of BCG vaccine used in Maputo was changed five times, and included products from the Japan BCG Laboratory, Connaught, and Pasteur. An outbreak of lymphadenitis in Inhambane Province in mid-1987, when only Pasteur BCG vaccine was in use, was associated with administration of twice the recommended dose (F. Cutts, personal communication, 1988).

Subsequently there has been another outbreak of lymphadenitis in Mozambique.⁷ Since this outbreak was positively associated with use of the Pasteur BCG vaccine in the new presentation, it is unlikely that its cause can be attributed to the same errors in dosage that were postulated for the previous outbreak.

Zimbabwe. One of the best documented reports of increased incidence of BCG-associated lymphadenitis comes from Zimbabwe.⁸ Beginning in the second half of 1986, sporadic reports indicated that an increasing number of children were developing regional lymphadenitis after BCG vaccination. A team was formed to investigate the extent of the problem and its possible causes. Available data showed that around 5% of those vaccinated in Harare developed regional BCG lymphadenitis, more than half of which was suppurative. A case definition was developed to characterize abnormal reactions, data were compiled on reported cases, case records were examined, and vaccination techniques were analysed. The following data were recorded for all cases of complications: date, date of birth, date of presentation, date and place of vaccination, site of vaccination, type of complications, and birth weight.

It was noted that the BCG vaccine in use at

⁷ See footnote g, p. 100.

⁸ *Report on the investigations of complications of BCG immunization, Zimbabwe, 1987.* Harare, Ministry of Health/WHO/Pasteur Vaccines, 1987.

vaccination centres was changed from the Mérieux product (derived from the Glaxo strain) to the Pasteur (Paris) vaccine during the second and third quarters of 1986. A similar increase in the frequency of complications had been observed in 1983 when Pasteur Vaccins products were also used for a brief period. It was planned to start using the Mérieux vaccine again in January, 1988, and recent information from Zimbabwe indicates that since autumn 1988 the incidence of lymphadenitis has declined.

A survey of the vaccination techniques employed indicated a number of deficiencies. Only 4 of 17 (24%) vaccine reconstitutions were correct, only 4 of 28 (14%) injections were carried out correctly, and in only 1 of 14 (7%) cases were both reconstitution and intradermal injection performed in the prescribed manner. The investigators concluded that the outbreak of BCG complications might have been caused by the incorrect procedures combined with a more reactogenic type of vaccine than had previously been used.

Zaire. In the second half of 1986, an increase in the number of cases of BCG adenitis was observed in Kinshasa, Zaire (54). The outbreak was investigated for the following possible causes: poor injection technique, incorrect dose, immunodeficiency of the recipients, and the preparation of vaccine used. Although the injection technique may have been poor and the incorrect dose may have been used, it was unlikely that all the 158 individuals who administered BCG vaccine would have changed their technique simultaneously. Moreover, 19 infants with BCG adenitis were examined and found to be HIV-seronegative.

A survey of the central vaccine stores indicated that in the autumn of 1985 the supplier of BCG vaccine had been changed from Glaxo to Pasteur Vaccins. The Pasteur vaccine would have been distributed from the end of 1985 and largely used in 1986, and it was therefore concluded that the outbreak was caused by the preparation of vaccine used.

The Caribbean. In late 1982 and early 1983 cases of severe BCG lymphadenitis were noted in Saint Lucia. Passive surveillance uncovered 37 cases (68). The immunization policy in Saint Lucia was to give BCG vaccine to 2–3-month-old infants. The mean attack rate was 3.4%, although this was higher in some clinics; immunization techniques were good, and the variation among the clinics was attributed largely to chance and perhaps to other factors such as inadequate mixing of freeze-dried vaccines. The outbreak occurred after a change to Pasteur vaccine.

Other countries. Outbreaks of BCG-associated lymphadenitis have also been reported to WHO from

Dominica, Jamaica, Kampuchea, and Rwanda. However, because of underreporting, it is likely that such outbreaks have occurred also in a number of other countries over the past 3 years.

Conclusions about recent outbreaks

Every reported outbreak of BCG lymphadenitis has occurred after a change in vaccine strain, in almost every case to the Pasteur (Paris) vaccine. Furthermore, all outbreaks of suppurative adenitis in national BCG vaccination programmes over the last 20 years have been connected with a change in vaccine.¹

Further investigation of these recent outbreaks is needed to clarify the role of possible confusion over the reconstitution and dosing instructions for Pasteur vaccine. Until January 1988, users of the Pasteur Vaccins BCG vaccine were instructed to reconstitute it to different concentrations, depending on whether newborns or older children were to be vaccinated. It is therefore possible that some health workers are confused and are still administering to newborns a full 0.1 ml of the vaccine reconstituted to normal strength according to the new instructions.

The study in Zimbabwe suggested that poor technique, in both reconstitution and administration of the vaccine, could contribute to the problem. This hypothesis is supported by the repeated field observations in Africa of the use of 1.0-ml tuberculin syringes to inject infants with BCG vaccine. Use of the same syringe to inject several children, following replacement of the needle between doses, is also not a rare practice and contributes to dosage inaccuracies. Thus, follow-up studies are needed to assess the impact on these outbreaks of training and changes in vaccine packaging.

Evaluation of the above reports suggests, however, that, notwithstanding the effect of poor administration technique, the preparation of BCG vaccine has been an important independent contributory factor in the recent cluster of outbreaks of BCG lymphadenitis.

It should be stressed, however, that all of the BCG vaccines employed, including the Pasteur (Paris) product, comply with current WHO requirements. At the same time it is apparent that the WHO requirements must be reviewed in order to address the problem of BCG vaccine reactogenicity.

Recommendations

Based on the information we have reviewed here, the recommendations outlined below can be made to maximize the effectiveness of BCG vaccination pro-

¹ BCG vaccination of the newborn. Rationale and guidelines for country programmes. Unpublished document WHO/TB/86.147.

grammes and to prevent further outbreaks of BCG-associated lymphadenitis.

Efficacy of BCG Immunization

There is good evidence that currently available BCG vaccines have an efficacy of 60–90% for disseminated tuberculosis or meningitis in young children, but somewhat lower for other forms of primary tuberculosis.

No BCG preparation tested was significantly more efficacious than any other under these conditions, and most of the preparations currently in commercial production have been tested at least once in a careful clinical trial. On the basis of protective efficacy, there is therefore no evidence at present to substantiate choosing one preparation or manufacturer of BCG vaccine over another. However, there is a need to develop a single *in vitro* test capable of predicting the induction of immune resistance of humans to infection or dissemination of *Mycobacterium tuberculosis*.

Prevention of BCG-associated lymphadenitis

- Because of the increasing number of outbreaks of BCG lymphadenitis in the last 4 years, changing the preparation of BCG vaccine supplied to a country where no problem has been encountered should be avoided.
- More research should be carried out to define better the exact dosage needed for optimal protection with fewer reactions. Furthermore, there is a need to devise tests that correlate with the higher reactivity of a given strain.
- The vaccine type and lot number in use in immunization programmes should be recorded by EPI programme managers, and training for this purpose should be extended to the local level.
- Training in BCG vaccination techniques should be re-emphasized, concentrating on the following: vaccine reconstitution to ensure proper homogenization; intradermal administration techniques; proper dosage; use of each syringe for a single child only; proper vaccine storage; and stock rotation to avoid use of vaccine after its expiry date.
- If there is a suspected increase in adverse reactions reported following BCG vaccination, active case-finding using a standard case definition should be initiated. The data collected should include the age at immunization, the sex and ethnic background of the recipient, the time till the onset of symptoms, the name of the vaccine manufacturer and lot number, the immunization site, and the conditions of storage of the vaccine.
- There is a need also to study the effect of outbreaks of BCG lymphadenitis on immunization drop-out

rates for infants who experience adenitis or who live in a community where this complication is reported.

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Résumé

Contrôle de la qualité des vaccins BCG par l'OMS: examen des facteurs susceptibles d'influer sur l'efficacité et l'innocuité du vaccin.

Depuis plus de 40 ans, c'est-à-dire depuis le moment où elle a pris la responsabilité de vastes programmes internationaux de vaccination par le BCG, l'Organisation suit la qualité de ces vaccins au moyen d'un système international de contrôle de la qualité qui comporte la distribution de lots de référence et de lots de semence de vaccin, la coordination des essais cliniques et de la vérification au laboratoire des lots de vaccins utilisés dans les programmes de vaccination, la formation, et la fourniture de conseils techniques dans le domaine de la production et du contrôle des vaccins BCG.

Des épreuves de laboratoire ont été conçues de façon à assurer la régularité de la production après qu'un produit ait fait l'objet d'essais cliniques et ait montré qu'il possédait les caractéristiques voulues. Ces essais portent sur la viabilité et la thermostabilité du vaccin ainsi que sur la production d'une hypersensibilité retardée chez l'animal.

La grande majorité (> 90 %) des vaccins BCG utilisés dans le monde sont produits à partir de trois souches: Pasteur-1173P2, Tokyo-172 et Glaxo-1077, même s'il existe au moins 15 grands fabricants utilisant des doses et des stabilisants différents dans l'élaboration de leurs produits. Les données dont on dispose sur les propriétés physico-chimiques de ces souches ne permettent pas de prévoir l'efficacité ou la toxicité des vaccins BCG. De plus, la sensibilité retardée à la tuberculine après vaccination chez l'enfant n'offre pas une corrélation entièrement satisfaisante avec l'efficacité du vaccin ou sa toxicité.

Dans un certain nombre d'études, on a tenté de déterminer l'efficacité des vaccins BCG. Lorsque ceux-ci sont administrés à des nouveau-nés, ils possèdent une forte efficacité contre les formes graves de tuberculose, pour lesquelles les critères de diagnostic sont plus rigoureux. Les données actuelles ne font apparaître aucune différence d'efficacité d'une préparation à l'autre.

En revanche, les réactions indésirables au vaccin diffèrent nettement d'une préparation à l'autre, notamment en ce qui concerne l'adénite régionale suppurée. Ainsi, la souche Pasteur-1173P2 est associée à un risque accru d'adénite par rapport aux souches Tokyo-172 et Glaxo-1077. Toutefois, il a été récemment suggéré que des facteurs liés à l'hôte, notamment l'âge et l'état immunitaire, pourraient jouer un rôle important dans l'incidence et le moment de l'apparition de ces réactions, de même que la dose et la technique d'administration. L'ostéite due au BCG varie également selon la préparation administrée et varie fortement selon la population à laquelle elle est administrée.

Dans tous les cas où on rapporte une incidence

accrue de réactions indésirables, il existe une association avec le remplacement du vaccin utilisé dans les programmes nationaux de vaccination. En raison de l'effet potentiellement défavorable des réactions post-vaccinales indésirables sur les programmes de vaccination, il est nécessaire d'éviter de changer de vaccin BCG sauf dans les cas où la préparation utilisée présente des inconvénients.

L'article présente des recommandations, notamment sur l'amélioration de la formation des agents chargés de la vaccination, pour une meilleure tenue des dossiers et en faveur du dépistage actif des cas afin d'aider les directeurs des programmes PEV à éviter ou à évaluer les problèmes liés à la réactogénicité du BCG.